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ORIGINAL ARTICLE

Study of neoadjuvant chemoradiotherapy with combined S-1 and low-dose cisplatin for patients with clinical stage II/III esophageal cancer

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KEYWORDS
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Summary *Background:* Trimodality therapy with surgery and neoadjuvant chemoradiotherapy (nCRT) has been developed to improve survival outcomes in advanced esophageal cancer. We hypothesized that the effect of surgery plus nCRT with oral fluoropyrimidine (S-1) and low-dose cisplatin will be effective with low toxic effects in patients with esophageal cancer as well as gastric cancer.
Methods: This cohort study included 28 Japanese patients who underwent nCRT plus esophagectomy for esophageal cancer in preoperative clinical Stage II/III. They received only one cycle of S-1 and low-dose cisplatin concurrently, followed by surgery 3–4 weeks after completion of nCRT (the doses of radiotherapy were 20 or 30 Gy). We examined the clinical efficacy and safety of nCRT plus esophagectomy.
Results: All patients had squamous cell carcinoma and they all completed nCRT and underwent esophagectomy. No treatment-related deaths were observed. The response rate to nCRT was 92.9%. The 1-year, 3-year, and 5-year overall survival rates were 84.4%, 67.0%, and 67.0%, respectively for Stage II/III.

Conflicts of interest: Kodai Takahashi, Hideto Ito, Masatoshi Hashimoto, Kazuhito Mita, Hideki Asakawa, Takashi Hayashi, Keiichi Fujino, and Yukihiro Hama have no conflicts of interest or financial ties to disclose.

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Conclusion: Toxicity of nCRT was acceptable, and the efficacy and prognosis were favorable, particularly as we performed only one cycle of neoadjuvant chemotherapy with low doses of radiotherapy.

1. Introduction

The prognosis of locally advanced esophageal cancer patients is poor. Trimodality therapy of surgical resection plus neoadjuvant chemoradiotherapy (nCRT) has been developed to improve survival outcomes of locally advanced esophageal cancer. Combination therapy appears to be more effective than either chemotherapy or radiotherapy alone because chemotherapeutic agents can act as radiosensitizers to improve locoregional control and prevent micrometastasis. Some previous reports have shown a survival benefit with the use of nCRT compared with surgery alone.[1–3]

Currently, the standard nCRT is fluorouracil (5-FU) and cisplatin in Japan. However, we administered oral fluoropyrimidine (S-1) and low-dose cisplatin for clinical Stage II/III esophageal cancer at our institution. S-1 has been approved in Japan for many malignancies, but limited data are available for esophageal cancer.[4] Recently, combination chemotherapy with S-1 and cisplatin has been widely studied in advanced gastric cancer.[5–7]

In 2008, an American Society of Clinical Oncology abstract showed that S-1 plus cisplatin was superior to continuous infusion of 5-FU plus cisplatin. Outside Asia, despite differences in S-1 dose and schedule from Asian trials, S-1 plus cisplatin was associated with fewer toxic effects, slightly improved survival, and equal efficacy when compared with 5-FU plus cisplatin.[8] Further, S-1 combined with low-dose cisplatin has been reported to be effective, with tolerable toxicity.[6]

We hypothesized that the effect of surgery plus nCRT with S-1 and low-dose cisplatin will be effective with low toxic effects in patients with esophageal cancer as well as gastric cancer. Therefore, the aim of this study was to clarify the efficacy and safety of nCRT plus esophagectomy for clinical Stage II/III esophageal cancer.

2. Materials and methods

2.1. Patients

All patients provided written informed consent. The study was approved by the Institutional Review Board to ensure the protection of patient privacy and confidentiality. The study was undertaken in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

This retrospective cohort study included 28 Japanese patients (5 females and 23 males; median age, 69.8 ± 8.3 years) who underwent nCRT plus esophagectomy for preoperative clinical Stage II/III esophageal cancer between January 2008 and April 2015 at our institution. All patients were staged preoperatively and postoperatively according to the tumor—node—metastasis classification of the American Joint Committee on Cancer Staging Version 7.[9] Prior to administering nCRT, all patients were staged by endoscopic ultrasound (EUS) and biopsy, computed tomography (CT), or positron emission tomography (PET). All pathological specimens from the initial endoscopic biopsies were read and confirmed by pathologists specializing in gastrointestinal malignancies. The eligibility criteria for this study were as follows: age $<$ 85 years, adequate organ function (white blood cell count $\geq$ 3500, hemoglobin $\geq$ 10 g/dL, aspartate aminotransferase/alanine aminotransferase $\leq 2 \times$ the upper limit of normal, platelet count $\geq$100,000/mm^3, serum creatinine $\leq$ 2.0 mg/dL), and a performance status of $<$2 at the time of admission. Exclusion criteria included the following: Patients with distant metastases and any previous palliative therapy or incomplete healing from previous major oncological surgery.

The patients received S-1 and low-dose cisplatin and nCRT concurrently, plus surgery. The medical data collected included those on patient characteristics, post-treatment characteristics, surgical outcome, clinicopathological findings, prognosis, and toxicity. Follow-up data were obtained from the patients' medical records and their referring physicians.

Postoperative complications were defined as complications occurring by postoperative Day 90. Postoperative mortality was defined as death occurring during hospitalization for the operation.

Toxicity was graded on the basis of the National Cancer Institute Common Terminology Criteria (NCI-CTC) guidelines.

Following nCRT and esophagectomy, postoperative pathological staging was compared to the initial staging to assess the effect of nCRT and subsequent downstaging or upstaging.

Pathological examinations included tumor detection and the assessment of invasion depth, metastatic lymph node number, and surgical margins. Tumor regression grades were defined by the Japan Esophageal Society as follows: Grade 3, markedly effective, with no viable cancer cells [pathological complete response (pCR)]; Grade 2, moderately effective, with viable cancer cells accounting for less than one-third of the tumor tissue (partial response); Grade 1, slightly effective, with viable cancer cells accounting for one-third or greater of the tumor tissue (low efficacy); Grade 0, ineffective, with no recognizable cytological or histological therapeutic effect (poor efficacy). Downstaging

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was defined as a reduction in either the T or N status in the pathological staging (ypTNM) compared with the clinical staging (cTNM).[10,11]

We examined the clinical efficacy and safety of nCRT plus esophagectomy for clinical Stage II/III esophageal cancer. The primary endpoints were overall survival (OS) and disease-free survival (DFS). The secondary endpoints were overall response rates (RR) and safety.

2.2. Chemotherapy regimen

All patients gave written informed consent before enrollment. Patients with no evidence of metastatic disease and good performance status were referred for surgical resection. All patients preoperatively received a regimen of S-1 plus low-dose cisplatin. One course of treatment consisted of 5-week cycles. Oral S-1 (80 mg/m^2 in two doses) was given daily for the first 3 weeks, followed by 2 weeks of rest. Low-dose cisplatin (10 mg) was given as a 6-hour infusion on Days 1—5 and Days 8—12 (10 days, total 100 mg). One chemotherapy cycle was administered before surgery.

2.3. Radiotherapy planning

All patients were treated with helical tomotherapy (Accuray, Tokyo, Japan), which is a novel treatment approach where the ring gantry irradiation geometry of a helical CT scanner is combined with an intensity-modulated megavoltage X-ray (6 mV) fan beam. An inverse treatment planning system was used to optimize the treatment plans. Radiotherapy treatment technique was administered at the discretion of the radiation oncologist; CT-based planning was performed with the patients lying supine with arms up on a Vac-Lock (Civco Medical Solutions, Kalona, IA, USA) immobilization device. Four-dimensional CT simulation scans were obtained to assess tumor motion during respiration. A clinical target volume (CTV) encompassing a 4—5 cm superior margin, 3—4 cm distal margin, and 2.5—3 mm radial margin was contoured. For upper thoracic tumors, bilateral supraclavicular lymphatics were included. For distal esophageal and gastroesophageal cancers, celiac nodes and nodes along the left gastric artery were always included in the CTV. For gastroesophageal junction carcinomas, other regional abdominal nodal groups were included on the basis of the magnetic resonance and/or PET—CT imaging findings. The prescribed dose was either 20 or 30 Gy (2 Gy/fraction) depending on the tumor size immediately before radiotherapy.

2.4. Surgical technique

Surgery was planned for 3—4 weeks following the completion of nCRT. All patients underwent restaging with EUS, CT, or PET 2—3 weeks following nCRT. Patients who did not show evidence of metastatic disease and who were deemed medically operable underwent esophagectomy. All patients underwent at least two field lymph node dissections and esophageal cancer in the upper and middle third of thoracic esophagus or lymph node metastasis in the superior mediastinum was essentially treated by cervical lymphadenectomy. Subsequently, the gastric tube was lifted via the posterior mediastinal route and cervical anastomosis of esophagus to gastric tube was accomplished.

2.5. Follow-up method

We confirmed that this dose schedule was tolerable in all patients. All patients were assessed every 3 months for the first 5 years after the completion of treatment. Routine follow-up exams included physical examination, history, and CT of the chest/abdomen. Endoscopy was performed if clinically indicated. CT of the chest/abdomen was performed routinely every 6 months.

2.6. Statistical analysis

Statistical analysis was performed using JMP 11 (SAS Institute Inc., Cary, NC, USA). The results were expressed as the mean $\pm$ standard deviation and percentage. Grouped data were expressed as the median (range) and nonparametric methods were used. Patients were followed up periodically until the last follow-up or death. OS was defined as the time from the date of the initial treatment to patient death. DFS was defined as the length of time after treatment during which no cancer was found. Differences between the cumulative survival rates of the tumor regression grades were calculated by the log-rank test for comparison using Kaplan—Meier survival curves. A p value of < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

All patients completed the nCRT regimen and underwent esophageal resection. No treatment-related deaths were observed. The median age was 69.8 $\pm$ 8.3 years. All patients had squamous cell carcinoma. The clinical stages of our patients before nCRT were Stage II in 10 patients (35.7%) and Stage III in 18 patients (64.4%). On examining the primary tumor location, upper thoracic tumors were found in 5 patients (17.8%), middle and lower thoracic tumors were found in 12 patients (42.9%), and 11 patients (39.3%), respectively. Four patients (14.3%) had T0/T1 lesions and 24 patients (85.7%) had T2/T3 lesions. Twenty patients had lymph node metastasis on CT at the time of diagnosis. The patients received two field lymph node dissections (46.4%) or three field lymph node dissections (53.6%). All procedures were performed following the guidelines provided by the Japan Esophageal Society. The mean operating time was 333.2 $\pm$ 23.9 min, and the mean intraoperative blood loss volume was 690.0 $\pm$ 6.7 mL. Other characteristics of the patients in this study are summarized in Table 1.

3.2. Perioperative complications

Perioperative complications were obtained through a standardized review of the surgery database at our institution. The severity of each postoperative complication

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Table 1 Patients characteristics.

Variables	$n = 28$
Gender (n, %)	
Male	23 (82.1)
Female	5 (17.9)
Age (years, mean ± SD)	69.8 ± 8.3
PS (n, %)	
0	18 (64.4)
1	10 (35.7)
BMI (kg/m^2, mean ± SD)	23.9 ± 3.2
Tumor location (n, %)	
Upper/middle/lower	5 (17.8)/12 (42.9)/11 (39.3)
Histology (n, %)	
Squamous/adenocarcinoma	28/0
cT stage (n, %)	
0	1 (3.5)
1	3 (10.7)
2	11 (39.3)
3	13 (46.4)
cN stage (n, %)	
0	8 (28.6)
1	12 (42.9)
2	5 (17.8)
3	3 (10.7)
Extent of lymphadenectomy (n, %)	
Two-field lymph node dissections	13 (46.4)
Three-field lymph node dissections	15 (53.6)
Operative time (minutes, mean ± SD)	333.2 ± 23.9
Intraoperative blood loss (ml, mean ± SD)	690.0 ± 6.7
Hospital stay (days, mean ± SD)	31.0 ± 9.5
cStage (n, %)	
II	10 (35.7)
III	18 (64.4)

was evaluated using the Clavien–Dindo classification.[12] Grade 0, no complications; Grade I, deviation from the normal postoperative course without the need for therapy; Grade II, complications requiring pharmacological treatments such as antibiotic administration; Grade III, complications requiring endoscopic, radiological, or surgical intervention; Grade IV, life-threatening complications requiring intensive care; Grade V, death. In the present study, the postoperative hospital mortality rate was 0%. Postoperative complications were observed in 10 patients (35.7%) and 25% of patients had Grade III complications. Anastomosis leakage was detected in three patients in this study. Pulmonary complications such as atelectasis, pneumonia, and pulmonary insufficiency were observed in four patients and chylothorax was observed in two patients. One patient underwent reoperation for chylothorax. No patients with Grade V complications were observed in this study. The patients' postoperative complications are summarized in Table 2.

Table 2 Postoperative mortality and morbidity.

Postoperative mortality and morbidity	Patients n (%)	Grade 3 n (%)
Hospital mortality	0	
Reoperation	1 (3.5)	
Overall morbidity	10 (35.7)	
Surgical site infection	1 (3.5)	0
Anastomotic leakage	3 (10.7)	3 (10.7)
Chylothorax	2 (7.1)	2 (7.1)
Transient recurrent nerve palsy	0	0
Pulmonary complication	4 (14.3)	2 (7.1)
Arrhythmia	0	0

3.3. Safety evaluation

In general, the patients tolerated nCRT well, and all patients completed treatment. No patients required dose reduction, and there were no nCRT-related deaths. The toxic effects of nCRT were evaluated using NCI-CTC. Hematological toxic effects included leukopenia, neutropenia, anemia, thrombocytopenia, renal dysfunction, and liver dysfunction. Nonhematological toxic effects included fever, fatigue, nausea, esophagitis, mucositis, and diarrhea. Twenty-five percent of the patients had ≥ Grade 3 toxicity, including leukopenia and thrombocytopenia. Leukopenia was the most common type of toxicity associated with nCRT (Grade 3; 14.3%) and nonhematological toxicity was mild. Nonhematological toxicity of Grades 3 and 4 was not observed in any of the patients. Radiation-related late toxicity was also not observed. Other toxic effects of nCRT are summarized in Table 3.

3.4. Clinical efficacy and survival

Complete resection (R0 resection) was successfully accomplished in all patients. Postoperative pathological staging determined that 22 patients (78.5%) were downstaged following nCRT, whereas no patients were upstaged.

Table 3 Toxic effects of nCRT.

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic toxicity				
Leukopenia	10 (35.7)	5 (17.9)	4 (14.3)	0
Anemia	10 (35.7)	4 (14.3)	0	0
Thrombocytopenia	4 (14.3)	2 (7.1)	3 (10.7)	0
Renal dysfunction	1 (3.5)	0	0	0
Liver dysfunction	0	0	0	0
Non-hematologic toxicity				
Fever	1 (3.5)	0	0	0
Fatigue	1 (3.5)	0	0	0
Nausea	1 (3.5)	0	0	0
Esophagitis	0	0	0	0
Mucositis	0	0	0	0
Diarrhea	0	0	0	0

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Grade 3 pCR of the primary tumor was achieved in 8 of 28 patients (28.6%) who underwent surgical resection. The RR to nCRT was 92.9%. The postoperative pathological stages were ypStage 0 in 4 patients (14.3%), ypStage I in 7 patients (25%), ypStage II in 14 patients (50%), and ypStage III in 3 patients (10.7%). The pathological tumor staging and effect of nCRT are shown in Table 4.

Table 4 Pathologic staging and effect of nCRT.

	Patients *n* (%)
ypT	
0	8 (28.6)
1	7 (25)
2	5 (17.8)
3	8 (28.6)
ypN	
0	17 (60.7)
1	6 (21.5)
2	4 (14.3)
3	1 (3.5)
ypStage	
0	4 (14.3)
I	7 (25)
II	14 (50)
III	3 (10.7)
Down-staging(+)	22 (78.5)
Pathologic effect of primary tumor	
Grade 1	2 (7.1)
2	18 (64.3)
3	8 (28.6)

The median follow-up of this cohort was 20 months (range, 1–83 months). The 1-year, 3-year, and 5-year OS rates were 84.4%, 67.0%, and 67.0%, respectively, for Stage II/III. The 1-year and 3-year OS rates were both 100% for Stage II, and the 1-year, 3-year, and 5-year OS rates were 71.8%, 57.4%, and 57.4%, respectively, for Stage III. The OS for all patients is shown in Figure 1. The 1-year, 3-year, and 5-year DFS rates were all 72.2% for Stage II/III. The 1- and 3-year DFS rates were both 100% for Stage II, and the 1-year, 3-year, and 5-year DFS rates were all 59.3% for Stage III. The DFS for all patients is shown in Figure 1.

4. Discussion

The aim of this study was to clarify the efficacy, prognosis, and safety of nCRT with S-1 and low-dose cisplatin plus esophagectomy for Stage II/III esophageal cancer. nCRT with S-1 plus low-dose cisplatin showed good efficacy and prognosis with acceptable toxicity. We administered nCRT with only one cycle of neoadjuvant chemotherapy and low doses of radiotherapy. Nevertheless, the efficacy and prognosis were favorable, with lower toxicity than that found in previous trials.[13–15]

In regard to efficacy, nCRT with only one cycle of chemotherapy (S-1 plus low-dose cisplatin), with low doses of radiotherapy (20 or 30 Gy) for clinical Stage II/III esophageal cancer patients contributed to a high RR for the primary tumor and metastatic lymph nodes. In this study, the RR to nCRT was 92.9%, pCR to nCRT was seen in 28% of patients in this study, which is similar to that seen in previous studies by Donahue et al (26%), Kesler et al (29.4%), and Courrech Staal et al (25.8%).[1,16,17]

Patients need to complete the full course of nCRT to achieve good efficacy and prognosis. In this study, all the

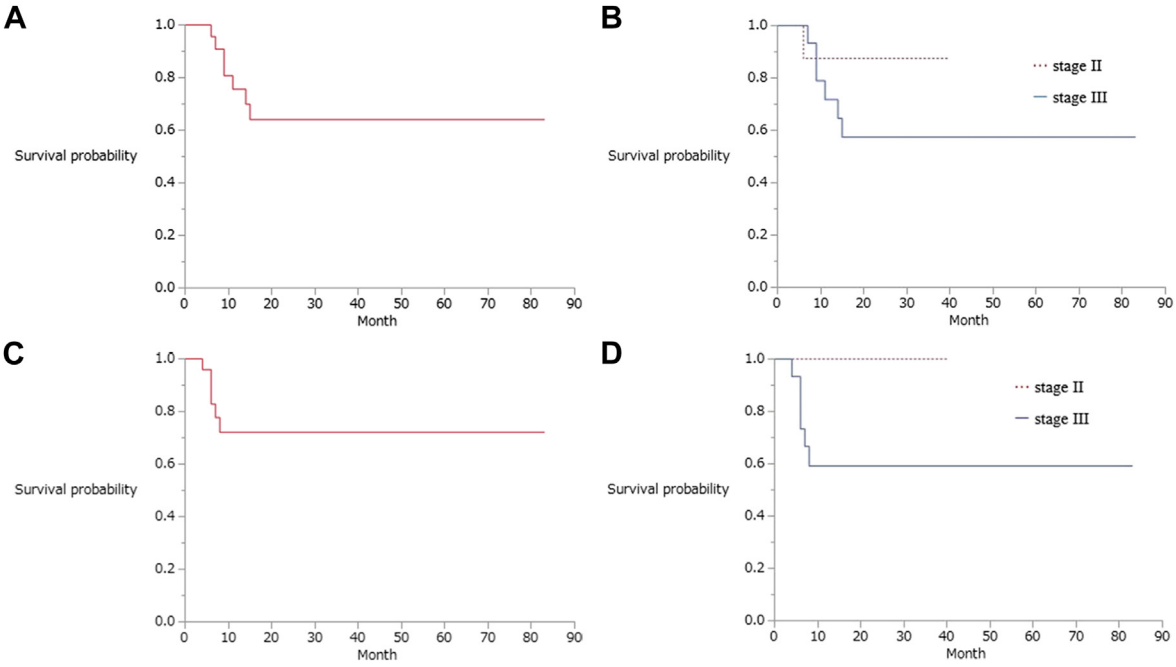

Figure 1 Kaplan–Meier curves of overall survival of (A) all patients and (B) clinical Stage II/III patients (C) Kaplan-Meier curves of disease-free survival of all patients and (D) clinical Stage II/III patients.

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patients completed nCRT, and no patients required dose reduction. There were also no nCRT-related deaths. The incidence of hematological and nonhematological toxicity was lower than those seen in previous trials using 5-FU and cisplatin regimens.[18,19] There are various reasons for the low toxicity observed in nCRT with S-1 plus low-dose cisplatin. First, this regimen used S-1. A previous study showed that S-1 had a greater effect on radiosensitivity in cancer treatment than 5-FU.[20] The doses of radiotherapy were 20 or 30 Gy in this study. However, the doses of radiotherapy were 40 to 60 Gy in other trial.[2] S-1 had a greater effect on radiosensitivity and thus, lower doses of radiotherapy could be used in the current study than in previous studies. Consequently, radiation-related toxicity was not observed in the present study because of the low doses of radiotherapy administered.[21]

Second, S-1 decreases gastrointestinal toxicity. S-1 is an oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine that combines three pharmacological agents: tegafur, a pro-drug of 5-FU; gimestat, which inhibits DPD activity; and potassium oxonate, which decreases gastrointestinal toxicity. S-1 can provide efficacious therapeutic plasma 5-FU concentrations by inhibiting DPD activity while decreasing gastrointestinal toxicity, which is one of the dose-limiting toxicities of 5-FU. In the present study, gastrointestinal toxicity $\geq$ Grade 3 was not observed. Recently, continuous 5-FU infusion has been replaced by the use of S-1 to avoid some of its adverse effects, particularly in stomach cancer.[22]

Finally, low-dose cisplatin decreases renal dysfunction compared with standard-dose cisplatin. Renal dysfunction is one of the most serious complications of cisplatin. A previous report showed that the advantages of low-dose cisplatin were a decreased risk of renal dysfunction, no need for hydration, and lower incidences of nausea.[23] Compared with high-dose regimens of cisplatin, low-dose cisplatin appears to be equally effective, with a lower risk of toxicity.[23]

The optimal time interval between nCRT and surgery is not well defined. Generally, for patients receiving nCRT, a 2- to 8-week interval between nCRT and surgery is widely accepted because it allows patients to recover from the toxicity of chemoradiotherapy.[24,25] The effect of nCRT is thereby maximized, and there is more tumor shrinkage and higher rates of pCR.[26,27] However, delaying surgery after nCRT completion raises the theoretical fears of tumor regrowth and dissection difficulties related to radiation-induced fibrosis, which may worsen surgical outcomes. A previous report showed that a longer interval between nCRT and surgery for esophageal cancer does not result in a better outcome.[1,28] There are theoretical concerns that if surgery is delayed, dissection could be more difficult because of increased radiation fibrosis.[29,30] In a previous randomized trial evaluating therapeutic approach, surgery was performed within 2—8 weeks after nCRT completion.[25] Although it is traditionally recommended to perform esophagectomy within 8 weeks after nCRT, we performed this surgery within 3—4 weeks after nCRT.

This study had some limitations inherent to observational studies. Firstly, in this study, the nonresponse group was very small, which may explain the high rate of partial response and pCR.

Next, this study was not a comparative review. We performed nCRT with S-1 and low-dose cisplatin plus esophagectomy for Stage II/III esophageal cancer. Hence, no patients received surgery alone or nCRT with other regimens.

Finally, this study was performed as a retrospective review in a single center with a limited number of patients. Moreover, only squamous cell carcinoma patients were enrolled. However, it is encouraging that our results are comparable with previously published data. In future, multicenter randomized controlled studies are required to determine the effect of neoadjuvant chemo-radiotherapeutic regimens.

5. Conclusion

In conclusion, the aim of this study was to clarify the efficacy and safety of nCRT plus esophagectomy for clinical Stage II/III esophageal cancer. Although we administered only one cycle of neoadjuvant chemotherapy with low doses of radiotherapy, the efficacy and prognosis were favorable, and low toxicity was observed. From our data, we conclude that this regimen is promising as nCRT for esophageal cancer.

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